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08/256,418

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/256,418	07/11/94	LASKY	L 833P1

EXAMINER

18M1/0609

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ART UNIT	PAPER NUMBER
1806	13

DATE MAILED: 06/09/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/30/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1,8-12, 15-26 is/are pending in the application.
Of the above, claim(s) 15-23 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1,8-12,26 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 12
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Applicant's amendment, filed 12/30/96 (Paper No. 11), is acknowledged.
Claims 2-7, 13, 14 and 27 have been canceled.
Claims 1, 8, 9, 11 and 26 have been amended.

Claims 15-25, drawn to the nonelected invention of Group II, have been withdrawn from consideration.

Claims 1, 8-12 and 26 are under consideration and being acted upon.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.
This Action will be in response to applicant's arguments, filed 12/30/96 (Paper No. 11).
The rejections of record can be found in the previous Office Action (Paper No. 7).

4. Applicant should update the status of the parent applications on the first line of the specification. USSN 08/056,454 is now abandoned.

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 7.

It is noted that applicant has amended the Brief Description of the Drawings to include Figure 2, however there is no Figure 2.

Applicant will submit formal drawings upon the indication of allowable subject matter.

6. Claims 1, 8-12 and 26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

A) Applicant has not disclosed how to use CD34-specific pharmaceutical compositions either alone (claims 1, 8 and 26) or in combination with other reagents (e.g. selectins, integrins, anti-inflammatories, etc., claims 9-11) as a therapeutic regimen for human diseases essentially for the reasons of record set forth in the last Office Action (Paper No. 7) and that addressed below in response to applicant's arguments.

Applicant's arguments, filed 12/30/96 (Paper No. 11) have been fully considered but are not found convincing. Applicant argues that the cancellation of claims 2-6, 13-14 and 27 renders the previous rejection moot, however the issues of record still apply to the instant claims. Applicant argues that in the absence of a 101 utility rejection, the instant methods are considered useful and that the instant disclosure and general knowledge in the pertinent art would not require undue experimentation to practice the instant invention. Applicant argues in conjunction with Puri et al. (J. Cell Biol., 1995) that CD34 is the predominant L-selectin ligand in the mixture of peripheral node addressins from human tonsil Applicant argues in conjunction with Kurohori et al. (Clinical Rheumatology, 1995) that there is a positive correlation between the expression of L-selectin on peripheral blood mononuclear cells of human RA patients and disease activity. Baumheuter et al. (Blood, 1994) disclose that CD34 is a physiologically significant ligand for L-selectin.

Applicant is reminded of the factors to be considered in determining scope and enablement ; 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986. The issues involved are whether or not the evidence of record was based on the expression of CD34 in murine and human tissues alone is generally recognized by those of skill in the art as being reasonably predictive of success in the anti-inflammatory therapeutic compositions and methods encompassed by the instant claims.

Applicant argues that Edgington, Ward et al. and Albelda ares not relevant since they were published before the identification of CD34 as the biologically relevant L-selectin ligand or do not address the use of native ligands of selectins as inhibitors (versus antibodies).

Applicant argues that amending the claims to recite the endothelial glycoform of native CD34 reflects the importance of the carbohydrate structure in the biological activity of CD34, which, in turn, obviates the concerns of Hemmerich et al..

Applicant argues that the use of isolated and purified CD34 polypeptide having the carbohydrate structure of native endothelial CD34 molecule obviates the limitations based upon the use of L-selectin-specific antibodies, disclosed in McMurray et al.

In contrast to applicant's assertions, it is noted that the instant specification discloses that changes in CD34 conformation oligomerization, glycosylation or translocation to the endothelial cell surface may determine the activity of CD34 (page 25, lines 30-34 of the instant specification). Also the specification discloses the importance of posttranslational carbohydrate modifications for high affinity L-selectin binding and that the protein backbone alone without the relevant sulfated carbohydrate ligand is insufficient to mediate lymphocyte trafficking (page 30, paragraph 2). CD34 is glycosylated differently in various endothelial cells (page 31, paragraph 1). Therefore, the instant disclosure is consistent with limitations on inhibiting leukocyte-mediated inflammation via isolated CD34 having the endothelial glycoform of native CD34, as different tissue-specific glycoforms exist and various structural constraints are critical to its role in L-selectin binding.

In contrast to applicant's assertions, the references of record were not limited to selectin-mediated antibodies. Edgington, Ward et al. and Albelda all disclose the limitations of polypeptides in inhibiting inflammatory responses. For example, Albelda et al. disclose the art-known limitation that the bioactivity of soluble adhesion receptors seems to be quite low (see page 509, Therapeutic Approaches). Edgington discloses the limitations of relying upon carbohydrate structures and the absence of in vivo results in determining selectin-mediated inhibition. The limitations of record on adhesion molecule-mediated inhibition of inflammatory do address the limitations of soluble receptors and carbohydrate structures as well as L-selectin-mediated adhesion as well as adhesion molecule-specific antibodies.

Applicant relies upon expression of CD34 alone and does not provide any working examples either in vitro or in vivo to support the therapeutic methods and compositions encompassed by the claimed invention. While the instant observations are consistent with the role of CD34 in L-selectin dependent trafficking to a diversity of organs and tissues in the mouse, the carbohydrate nature, the tissue/structural diversity of CD34 and conformational constraints of the L-selectin ligand presented by CD34 presents limitations to the use of CD34 as a therapeutic composition. It is not clear how strong or how relevant such interactions are associated with leukocyte homing in vivo either in normal or disease conditions. There is insufficient information or nexus that either CD34 or L-selectin expression alone in murine and human tissues would be predictive for targeting the claimed CD34 specificities to inhibit pathological conditions associated with L-selectin-CD34 interactions, commensurate in scope with the claimed invention. The claimed invention is drawn to modulating human disease through L-selectin-CD34 interactions, however applicant has disclosed only limited information concerning such interactions in mouse experimental systems and not with isolated CD34 having the endothelial glycoform of native CD34. The criticality of L-selectin-CD34 interactions in leukocyte-CD34 interactions, particularly in vivo under disease conditions, has not been demonstrated. Furthermore, it is not clear that the distribution and expression of CD34 in human tissues would provide sufficient targeting for the range of diseases targeted by the claimed methods. For example, tissue expression of CD34 may not be sufficient to block human leukocytes from adhering to endothelium associated with all of the acute and

chronic inflammatory conditions claimed. There is insufficient information whether human leukocyte-mediated inflammation would operate through other known adhesion pathways to mediate inflammatory conditions that would obviate any inhibition through a CD34-mediated pathway. Therefore, the specification fails to enable the critical role or targeting CD34 in inhibiting human disease.

There appears to be insufficient evidence that applicant's reliance on the either L-selectin or CD34 expression alone would indicate that the claimed therapeutic modalities based upon CD34-specific antagonists would operate on either acute or chronic diseases, commensurate in scope with the claimed invention. Although an adhesion molecule-receptor pair may be expressed and play a role in leukocyte accumulation in various inflammatory conditions, the ability of an adhesion molecule antagonist to affect some therapeutic endpoint will depend on the adhesion molecule antagonist and the nature of the disease (e.g. acute versus chronic, tissue specificity, etc.). In humans, the claimed diseases encompassed by the claimed methods are already established before therapy is offered. There are distinct differences in the adhesion requirements for particular types of inflammation.

Different adhesion molecule specificities are appropriate for different acute and chronic inflammatory conditions. Applicant has not provided sufficient direction or guidance to indicate what are the appropriate combinations of CD34-specific antagonists to treat the pathological conditions encompassed by the claimed invention. Therefore, in addition to the lack of predictability of treating the claimed pathological conditions with CD34-specific antagonists; there appears a lack of predictability of treating the claimed pathological conditions with CD34-specific antagonists in combination with selectin/integrin-specific inhibitors or anti-inflammatory reagents without more direction from the instant specification.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting cell/leukocyte-endothelial cell interactions.

B) It is unclear from the specification what is encompassed by claim 9's recitation of selectin, selectin ligand, an integrin, an integrin ligand, ligand other than CD34 polypeptide, or antibodies to such molecules. Also, there is no evidence that such claimed compounds work as effective therapeutic agents in humans nor is there evidence that such compounds would work in combination with CD34-specific therapeutic agents. The disclosure is not enabled for the claimed methods using any selectin, integrin, etc., all of which are embraced by claim 9. Compositions comprising any of these compounds do not necessarily correlate with their ability to inhibit human pathology. The specification has not provided sufficient

direction or guidance to one of skill in the art to properly select or administer any selectin, integrin, etc. that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods using the teaching of the specification alone.

Applicant's arguments, filed 12/30/96 (Paper No. 11), have been fully considered but are not found convincing. Although applicant has canceled the recitation of non-protein antagonists, the claims read on any number of combinations with native CD34. For the reasons of record and the issues presented above in section A; the specification has not provided sufficient direction or guidance to one of skill in the art to properly select or administer any selectin, integrin, etc. that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods using the teaching of the specification alone. There are distinct differences in the adhesion requirements for particular types of inflammation

C) Applicant's amendment, filed 12/30/96 (Paper No. 11), cancelling the recitation of MECA-79 has obviated the previous deposit requirement under 35 U.S.C. § 112, first paragraph.

7. Applicant's amendment, filed 12/30/96 (Paper No. 11), cancelling the recitation of "a non-protein antagonist of L-selectin-CD34 interaction" has obviated the previous rejection under 35 U.S.C. § 112, first and second paragraphs.

8. Claims 1, 8-12 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8-12 and 26 are indefinite in the recitation of "L-selectin-mediated inflammation" and "a therapeutically effective amount" because it is not clear what is "L-selectin-mediated inflammation" and what constitutes "a therapeutically effective amount". Inflammation is a protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or sequester both the injurious agent and the injured tissue While it includes a complex series of events including leukocyte-endothelial adhesion and leukocyte migration, inflammation is not caused or mediated by an adhesion molecule. The claims fail to state the function which is to achieved.

The amendments must be supported by the specification so as not to add any new matter.

9. Claims 1, 8, 12, and 26 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Butcher et al. (U.S. Patent No. 5,538,724; see entire document) essentially for the reasons of record set forth in the last Office Action (Paper No. 7).

Applicant's arguments, filed 12/30/96 (Paper No. 11), have been fully considered but are not found convincing. Applicant argues that Butcher et al. teaches the use of MECA-79 antibody and the instant claims are now directed towards a particular glycoform of CD34 polypeptide. Butcher et al. teaches the use of modulating leukocyte extravasation associated with inflammatory diseases encompassed by the claimed inventions (e.g. columns 3-6, Table 1) with soluble forms of the addressin identified by MECA-79 (e.g. column 5, paragraph 2) and various formulations and combinations of said antagonists (columns 3-6). The claimed and referenced methods and compositions appear to be the same. Although the reference is silent about the CD34 specificity, the addressin identified by MECA-79 is the same as the claimed CD34 specificity. Applicant has not shown an unobvious difference between the claimed and disclosed methods and compositions. Applicant's arguments are not found persuasive.

10. Claims 1, 8, 12 and 26 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Lasky et al. (U.S. Patent No. 5,304,640) essentially for the reasons of record set forth in the last Office Action (Paper No. 7).

Applicant's arguments, filed 12/30/96 (Paper No. 11), have been fully considered but are not found convincing. Applicant acknowledges that the 90kD murine protein referred to as Sgp90 disclosed in Lasky et al. is the substantially identical with murine CD34. However applicant argues that the thrust of the reference is GlyCAM-1 and not the role of the 90 kD protein and that the biological role of 90 kD ligand was not determined until the present invention was made. However, Lasky et al. clearly teaches the use L-selectin ligand Sgp90 antagonists including soluble Sgp90 to treat inflammatory conditions encompassed by the claimed invention (see entire document, including section K. Therapeutic Compositions) . Applicant has not show the unobvious difference between the claimed and disclosed methods and compositions.

Applicant has indicated that a Declaration under 37 CFR 1.132 may be provided to obviate this rejection.

11. Claims 1, 8-11 and 26 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) in view of Lasky et al. (CSHSQB, 1992; 1449, #35), Berg et al. (J. Cell Biol., 1991; 1449, 1449, #8) or Imai et al. (J. Cell Biol. 1991; 1449, #28), Sutherland et al. (Leukemia, 1988; 1449, #51), Lasky et al. (U.S. Patent No. 5,098,833; 1449, #2), Watson et al. (Nature, 1991; 1449, #55), Fina et al. (Blood, 1990; 1449, #22) and Schlingemann et al. (Lab. Invest., 1990; 1449, #42) essentially for the reasons of record set forth in the last Office Action (Paper No. 7).

Applicant's arguments, filed 12/30/96 (Paper No. 11), have been fully considered but are not found convincing. Applicant's arguments and the examiner's rebuttal concerning Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) are set forth above in sections 10-11. In addition, applicant argues that Lasky et al. (CSHSQB) focuses on the identification of GlyCAM-1 as an L-selectin ligand and are uncertain about the 90 kD molecule. Although there was speculation about the exact role of the 90 kD molecule in inflammation, this reference clearly directs its role to leukocyte adhesion and migration as well as inflammation. Applicant argues that the secondary references are less specific than the primary references. However, the combination of references including the secondary references clearly teach the role of 90 kD (CD34) in leukocyte adhesion and teach inhibiting such interaction and its role in inflammation with 90 kD-specific antagonists, including the use of soluble 90 kD. Applicant's arguments ar not found persuasive.

12. Claims 9-11 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) in view of Lasky et al. (CSHSQB, 1992; 1449, #35), Berg et al. (J. Cell Biol., 1991; 1449, 1449, #8) or Imai et al. (J. Cell Biol. 1991; 1449, #28), Sutherland et al. (Leukemia, 1988; 1449, #51), Lasky et al. (U.S. Patent No. 5,098,833; 1449, #2), Watson et al. (Nature, 1991; 1449, #55), Fina et al. (Blood, 1990; 1449, #22) and Schlingemann et al. (Lab. Invest., 1990; 1449, #42) as applied to claims 1-14, and 26-27 above and in further view of Spertini et al. (J. Immunol., 1991; 1449, #45), Carlos et al. (Immunol. Rev., 1990; 1449, #17), Heavner et al. (U.S. Patent No. 5,464,935) and Butcher (Cell, 1991; 1449, #16) essentially for the reasons of record set forth in the last Office Action (Paper No. 7). .

Applicant's arguments, filed 12/30/96 (Paper No. 11), have been fully considered but are not found convincing. Applicant's arguments and the examiner's rebuttal rely upon the issues presented above in sections 11.
The use of a CD34-specific pharmaceutical composition in combination with other reagents (e.g. selectins, integrins) as a therapeutic regimen for human diseases would have been obvious to one of ordinary skill at the time the invention was made. .

13. No claim is allowed.

14. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

16. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
June 3, 1997

LILA FEISEE
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